CTU Protocol

A multi-centre, randomised, controlled trial evaluating the effects of early high-dose cryoprecipitate in adult patients with major trauma haemorrhage requiring major haemorrhage protocol (MHP) activation

CRYOSTAT-2
Early cryoprecipitate in trauma

Version: 4.0

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Protocol Development Group:

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Karim Brohi	QMUL	*KB, SS, RD, NC conceived of the study.* *KB, RD, NC, SS, JBe, LGr initiated the study design and AD, JBr and CF helped with implementation.* *KB is the grant holder.* *DC, HT provided statistical expertise in clinical trial design and will oversee the statistical analysis.* *SM provided health economic expertise.* *All authors contributed to refinement of the study protocol and approved* the final version
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CTU Protocol

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General Information

This document was constructed using the National Health Service Blood and Transplant Clinical Trials Unit (NHSBT CTU) Protocol Template FRM4468 Version 1.0, which is based on the MRC CTU Protocol template Version 4.0 and the SPIRIT guidelines 2013.(1, 2) It describes the CRYOSTAT-2 trial, coordinated by the NHSBT CTU and provides information about procedures for entering patients/participants into it. The protocol should not be used as an aide-memoire or guide for the treatment of other patients. Every care has been taken in drafting this protocol, but corrections or amendments may be necessary. These will be circulated to the registered investigators in the trial, but sites entering participants for the first time are advised to contact the Trial Manager to confirm they have the most up to date version.

Compliance

The trial will be conducted in compliance with the approved protocol, the Declaration of Helsinki the Principles of Good Clinical Practice (GCP), European Commission Directive 2005/28/EC with the implementation in national legislation in the UK by Statutory Instrument 2004/1031 and subsequent amendments, the UK Data Protection Act 2018, the National Health Service Research Governance Framework for Health and Social Care (RGF) and any other applicable national regulations.

Queen Mary University of London (QMUL) and NHSBT have a responsibility as joint data controllers to ensure compliance with the General Data Protection Regulation (GDPR) and Section 251 of the NHS Act 2006 (originally Section 60 of the Health and Social Care Act 2001), which provides the statutory power to ensure that NHS patient identifiable information needed to support essential NHS activity can be used without the consent of patients.

Sponsor

The Queen Mary, University of London (QMUL) is the primary trial sponsor and has delegated responsibility for the overall management of the CRYOSTAT-2 trial to the NHSBT CTU. Queries relating to the QMUL sponsorship of the trial should be addressed to: Tumi Kaminskas, JRMO, Research Services, Dept. W, 69-89 Mile End Road, London, E1 4UJ, E-mail: research.governance@qmul.ac.uk.

Funding

This is a study funded by NIHR Health Technology Assessment Board – grant number: 15/57/02 and Bart's Charity.

Authorisations and Approvals

This trial was approved by the National Institute of Health Research and is, therefore, part of the Clinical Research Network Portfolio of Studies. The Health Research Authority (HRA) has approved the study in the UK. This protocol is compliant with the Mental Capacity Act (Northern Ireland) 2016.

Trial Registration

This trial has been registered with the International Standard Randomised Clinical Trials Register, where it is identified as ISRCTN 14998314

Trial Administration

Please direct all enquiries to the Trial Manager in the first instance. Clinical queries will be passed to the Chief Investigator via the Trial Manager.

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For full details of Trial Committees, please refer to Section 0

Study Synopsis

Scientific title of clinical study	A multi-centre, randomised, controlled trial evaluating the effects of early high-dose cryoprecipitate in adult patients with major trauma haemorrhage requiring major haemorrhage protocol (MHP) activation.
Public title of clinical study	Early cryoprecipitate for severe bleeding after trauma.
Protocol Short Title/Acronym	CRYOSTAT-2: early cryoprecipitate in trauma.
Protocol Version and Date	Version 4.0 15/02/2022
Primary Sponsor	QMUL
Funder	NIHR Health Technology Assessment Board
ISRCTN	14998314
Date Study Registered	24/04/2017
Study design	• Interventional phase III study • Multi-centre, interventional, randomised, unblinded, parallel controlled trial • Participants will be randomised 1:1 via opaque sealed envelopes held securely in participating EDs • The study will be run and conducted at sites in UK and USA.
Health Condition(s) or Problem(s) Studied	Major trauma haemorrhage
Key inclusion and exclusion criteria	***Inclusion criteria*:** Patients are eligible for this trial if: *1.* The participant is judged to be an adult, aged 16 years or older in the UK (or according to local guidance) and has sustained severe traumatic injury 2. The participant is deemed by the attending clinician to have active haemorrhage *AND REQUIRES:* 3. Activation of the local major haemorrhage protocol for management of severe blood loss *AND HAS STARTED or HAS RECEIVED:* 4. at least one unit of any blood component ***Exclusion criteria:*** A patient will not be eligible for this study if he/she fulfils one or more of the following criteria: 1. The participant has been transferred from another hospital 2. The trauma team leader deems the injuries incompatible with life 3. More than 3 hours have elapsed from the time of injury

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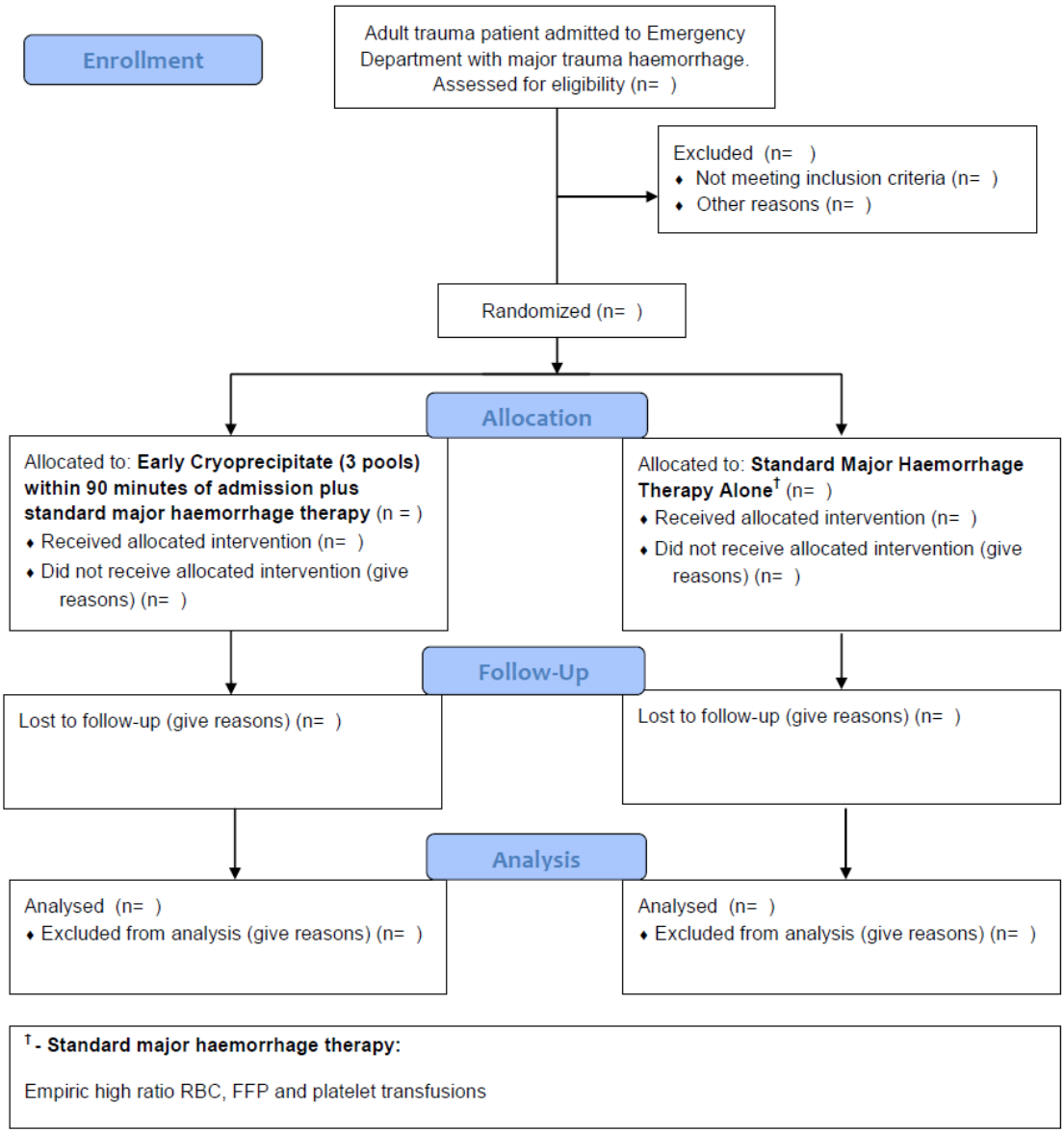
Setting	Emergency departments, operating theatres and intensive care units of participating trauma centres
Interventions to be compared	***Intervention arm:*** Early intravenous infusion of cryoprecipitate (3 pools of cryoprecipitate – the equivalent to 15 single units of cryoprecipitate or 6g fibrinogen), within 90 minutes of arrival at hospital in addition to standard major haemorrhage therapy ***Comparator arm:*** Major haemorrhage therapy alone
Study hypothesis	Major bleeding after injury is exacerbated by a clotting abnormality – 'acute traumatic coagulopathy' (ATC). ATC is characterised by hypofibrinogenaemia and fibrinolysis. Early replacement of fibrinogen will treat the coagulopathy and may reduce bleeding and improve outcomes. This study will evaluate whether early fibrinogen supplementation in the form of cryoprecipitate (equivalent of 6g fibrinogen replacement) during major traumatic haemorrhage will reduce mortality.
Primary outcome measure(s)	All-cause mortality at 28 days
Key Secondary outcome measure (s)	1. All-cause mortality (including death from bleeding) at 6 hours, 24 hours, 6 months and 12 months from admission 2. Death from bleeding at 6 hours and 24 hours 3. Transfusion requirements, in numbers of units, for RBC, platelets, FFP & cryoprecipitate at 24 hours from admission, including pre-hospital transfusion 4. Destination of participant at time of discharge from hospital 5. Quality of life measures: EQ5D-5L and Glasgow Outcome Score at discharge/day 28 and 6 months after injury 6. Hospital resource use up to discharge or day 28, including ventilator days, hours spent in critical care and in-patient stays. 7. Symptomatic thrombotic events
Duration of Study	Duration of set up – 4 months to obtain all ethical/regulatory approvals, finalise contracts, prepare essential documents and study database and start to initiate study centres. Duration of recruitment – The trial is expected to recruit from UK and US sites until the target of 1600 participants is reached, based on an average recruitment rate of 1.5 participants/month at each UK MTC (n = 25) and Level 1 trauma centres in USA (n=1.

	Duration of follow-up for each participant will be 12 months. Duration of study close-out – 8 months to complete all data cleaning and statistical analysis and site close out. The planned total trial duration is 66 months.
Countries of recruitment	UK and USA.
Target Sample Size	800 participants per arm
Date of first enrolment	1st July 2017
Contact Details for Public Queries	Claire Foley 07823 351738 claire.foley@nhsbt.nhs.uk
Contact Details for Scientific Queries	Professor Karim Brohi 020 7882 2483 k.brohi@qmul.ac.uk
Lay Summary of Study	Bleeding is a major cause of death in severely injured patients. Many of these patients rapidly develop an abnormality of the clotting system, known as 'acute traumatic coagulopathy' (ATC). The two most important abnormalities in ATC are a low fibrinogen and increased clot breakdown. It has been hypothesised, and there are some non-randomised studies that show, that treatment of trauma patients who are bleeding with fibrinogen therapy stops bleeding more effectively than standard care, reduces transfusion needs and may reduce death rates. This study will look at the effects of transfusing early high dose cryoprecipitate (which is a concentrated source of fibrinogen), to adult trauma patients with severe bleeding within 90 minutes of arrival at hospital. This study will evaluate whether early cryoprecipitate reduces death rates when major bleeding occurs after injury.

Study Schema



Contents

Abbreviations and Glossary

AE	Adverse Event
AIS	Abbreviated Injury Scale
AR	Adverse Reaction
ARDS	Acute Respiratory Distress Syndrome
ATC	Acute Traumatic Coagulopathy
CI	Chief Investigator
CLRN	Comprehensive Local Research Network
COM	Clinical Operations Manager
CRF	Case Report Form
CTCOFR	Composite Time To Organ Failure Resolution
CTU	NHSBT Clinical Trials Unit
DCR	Damage Control Resuscitation
DH	Department Of Health
DM	Data Manager
DMC	Data Monitoring Committee
DPA	Data Protection Act
DVT	Deep Venous Thrombosis
ED	Emergency Department
Fg	Fibrinogen
FgC	Fibrinogen Concentrate
FFP	Fresh Frozen Plasma
GCP	Good Clinical Practice
GCS	Glasgow Coma Scale
GDPR	General Data Protection Regulation
GP	General Practitioner
HE	Health Economics
HDU	High Dependency Unit
HR	Haemostatic Resuscitation
HRA	Health Research Authority
IB	Investigator's Brochure
ICF	Informed Consent Form
ICU	Intensive Care Unit
ISRCTN	International Standard Randomised Controlled Trial Number
IRAS	Integrated Research Application System
ISS	Injury Severity Score
MHP	Major Haemorrhage Protocol
MI	Myocardial Infarction
MOF	Multiple Organ Failure
NHS	National Health Service
NHSBT	NHS Blood and Transplant
NI	Northern Ireland
NIHR	National Institute for Health Research
ONS	Office for National Statistics
PALS	Patient Advice and Liaison Service
PDS	Patient Demographic System
PE	Pulmonary Embolism
PI	Principal Investigator
PIS	Patient Information Sheet
PROMs	Patient Reported Outcome Measures

QA	Quality Assurance
QC	Quality Control
QMUL	Queen Mary, University of London
QoL	Quality Of Life
RBC	Red Blood Cells
RCT	Randomised Controlled Trial
R&D	Research And Development
RN	Research Nurse
RR	Respiratory Rate
SABRE	Serious Adverse Blood Reactions And Events
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SBP	Systolic Blood Pressure
SHOT	Serious Hazards Of Transfusion
SOP	Standard Operating Procedure
STRAR	Serious Transfusion Related Adverse Reaction
SSI	Site Specific Information
TARN	The Trauma Audit and Research Network
TBI	Traumatic Brain Injury
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
TXA	Tranexamic Acid

Background

Introduction

Worldwide, trauma accounts for 5.8 million deaths every year [1], equivalent to one death every nine minutes and it is the leading cause of death in persons under the age of 44. The impact on life years lost is significant and equal to the life years lost from cancer, heart disease and HIV combined. Bleeding accounts for 40% of all injury-related deaths, many within hours of injury and there is a high burden of major haemorrhage for both patients and the NHS. A recent NIHR PgfAR [2] identified that approximately 7780 people suffer major haemorrhage in England & Wales each year, of which an estimated 2800 will die, at a total cost of nearly £150m to the NHS [3]. This value does not include any societal effects, such as lost working days. The lost economic output to the UK annually from death and disability has been estimated to be up to £3.7 billion [4].

25% of all trauma patients have abnormal blood clotting known as acute traumatic coagulopathy (ATC), which causes higher rates of bleeding, major haemorrhage and a three- to four-fold increased risk of death [5]. There are two main clotting abnormalities in ATC: low fibrinogen levels [6] and increased clot breakdown (fibrinolysis) [7]. Data from over 500 trauma patients in the NIHR PGfAR study [2] have established that low fibrinogen levels are common at hospital admission and are independently associated with 24 hour and 28 day survival. Fibrinogen is the key pro-coagulant factor needed for stable clot formation. It forms insoluble fibrin strands, is the ligand for platelets and forms the haemostatic plug at sites of bleeding. Fibrinogen is the earliest coagulation protein to fall during active major bleeding [8], and this abnormality will limit the formation of stable clots.

The beneficial effects of correcting fibrinolysis in trauma haemorrhage have been addressed in a global RCT - CRASH-2. This study evaluated the effects of an anti-fibrinolytic drug, tranexamic acid (TXA) on mortality [9]. CRASH-2 data have not only confirmed the importance of TXA therapy as a means to improve clinical outcome, but have also shown that it is vital to deliver haemostatic therapy early (i.e. within 3 hours of injury) [10]. This has been confirmed with the recent findings from the PROPPR study [11].

Trauma patients who present to hospital with major haemorrhage are treated using an integrated approach known as damage control resuscitation (DCR). This focuses on 1) diagnostic and treatment pathways aimed at identifying and stopping on-going bleeding e.g. emergency surgery or interventional radiology and 2) best supportive care, known as ‘haemostatic resuscitation’ – which includes blood transfusion (using major haemorrhage protocols (MHP)), reversal of blood acidosis and active re-warming of patients. Haemostatic resuscitation is defined by the early (empiric) and simultaneous delivery of RBCs and FFP in high ratio and in conjunction with TXA [12,13]. Low dose fibrinogen supplementation (in the form of cryoprecipitate in the UK) is recommended as part of the treatment for major haemorrhage in national guidelines [12] although therapy is often triggered by fibrinogen blood results. In a recent UK epidemiological study conducted at 22 trauma centres and units across England & Wales [14] significant delays in the administration of cryoprecipitate to bleeding trauma patients were reported (median time for cryoprecipitate administration - 184 minutes), by which time 25% of patients had died.

This trial will evaluate the effects of early administration of high dose cryoprecipitate (within 90 minutes of arrival at hospital) when used as treatment for major trauma haemorrhage. The primary endpoint will be all-cause mortality at day 28. Secondary measures will

include: transfusion requirements, total ventilator days, hospital stay including ICU/HDU stay up to study day 28, all-cause mortality (up to 12 months) and safety measures evaluating arterial and venous thrombotic events up to study day 28 (or date of discharge from an acute care facility, whichever is the sooner). Quality of life measures will include: destination of patient at discharge from hospital; Glasgow Outcome Score and EQ5D-5L at discharge and at 6 months post-injury. Hospital resource use up to discharge or day 28 will be calculated.

Summary of existing knowledge

Early clinical data suggest that fibrinogen supplementation may improve outcomes for trauma haemorrhage, by improving clot strength [15], reducing blood loss [16,17] and increasing survival [18]. In an uncontrolled observational study of 131 haemorrhagic patients, mortality rates were reported to fall by 14% after fibrinogen treatment [18]. Two observational cohort trauma studies [19-21] have also reported reduction of mortality in patients receiving higher fibrinogen content during massive transfusion therapy. Despite very high doses of fibrinogen supplementation (up to 12g), plasma levels did not increase beyond the normal range in health and there were no reported adverse events [18].

Recent systematic reviews appraising the management of major bleeding, focusing on transfusion therapy and the use of fibrinogen supplementation, have been published [22-24]. A Cochrane review evaluating the effectiveness of fibrinogen concentrate for bleeding patients found six small trials in elective surgery, all of low quality and underpowered for mortality but with a clear reduction in the incidence of allogeneic transfusions (RR 0.47, 95% CI 0.32 to 0.72) [23]. Twelve completed fibrinogen concentrate trials have been identified in an ongoing Cochrane review evaluating pro-haemostatic agents [25], but none in trauma. There are five small ongoing RCTs in trauma which are evaluating fibrinogen concentrate (NCT01475344), (NCT02203968), (NCT02344069), (NCT01545635), (EudraCT2015 - 000875-28), aiming to recruit 300 patients in total. All use surrogate outcomes and none evaluate mortality. There are no other trials evaluating cryoprecipitate in trauma outwith the feasibility trial CRYOSTAT1.

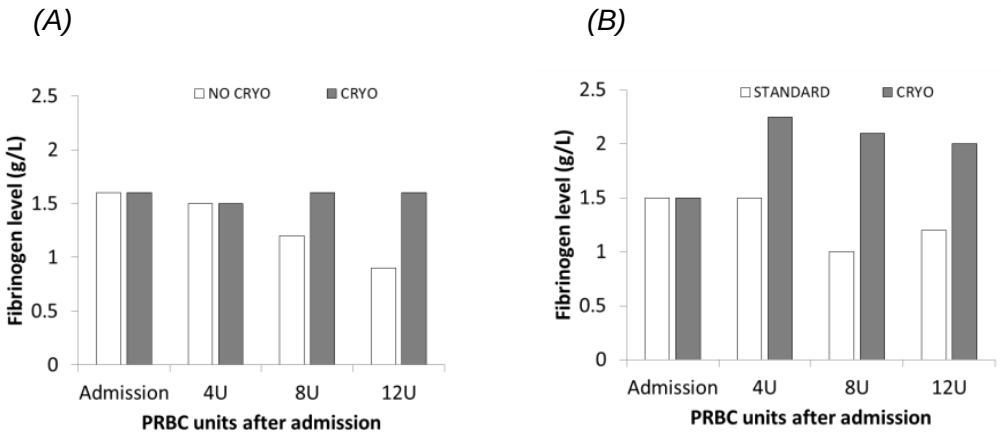
A feasibility RCT evaluating the early use of cryoprecipitate in major trauma haemorrhage has been completed (CRYOSTAT1) [26]. This study demonstrated that it was possible to conduct a randomised trial in 43 adult trauma patients with severe bleeding at two major trauma centres in the UK (Royal London Hospital and John Radcliffe, Oxford) with a parallel study conducted by the UK military at Camp Bastion, Afghanistan. Although not powered for clinical outcomes, the results confirmed that it was feasible to deliver cryoprecipitate within 90 minutes of admission and also suggested that early cryoprecipitate therapy maintained blood fibrinogen levels above 1.8 g/L during active bleeding with a signal for reduced mortality (2 deaths vs. 6 deaths) in the treatment arm of the study. Of particular interest to this study was that patients entered into the CRYOSTAT study in both intervention and comparator arms had mean blood fibrinogen levels at admission of 1.55 g/L, i.e. within the normal range. Treatment with early cryoprecipitate raised the fibrinogen blood levels during the first haemorrhagic episode, but by 24 hours there was no difference in fibrinogen levels between arms. In addition, no thrombotic events were seen in the intervention arm. This feasibility trial emphasised the importance of pragmatic inclusion criteria and a simple case report form for focused outcome and adverse event data collection.

There are two main sources of fibrinogen replacement: cryoprecipitate and fibrinogen concentrate. A recent systematic review comparing the efficacy of cryoprecipitate and

fibrinogen concentrate reported a scarcity of high quality data [27]. However, the four included studies (three observational, 1 RCT) showed no difference in fibrinogen increment; transfusion requirement; thromboembolic events or bleeding between the products. *In vitro* and *ex vivo* work have also shown that these two blood products lead to similar improvements in coagulopathy during trauma haemorrhage and the effects are dependent on fibrinogen concentration rather than formulation [6]. Cryoprecipitate is one quarter of the cost per gram of fibrinogen and a recent economic evaluation confirmed that even after cryoprecipitate wastage, fibrinogen concentrate is at least twice as expensive [28].

Need for a trial

Fibrinogen levels are lower in trauma patients who present to hospital with coagulopathy and bleeding and are an independent predictor of mortality at 24 h and 28 days [6]. Fibrinogen is known to be rapidly depleted during major traumatic haemorrhage (Figure A) and recent work has shown that it is not restored despite the use of haemostatic resuscitation.



(A) Fibrinogen is low immediately on admission and falls precipitously during MHP transfusion of RBC units (U) without supplementation. (B) In the CRYOSTAT1 trial early supplementation with fibrinogen (cryoprecipitate) was able to restore fibrinogen levels to the recommended range (>2 g/L) by the time of administration of the 4th RBC unit.

In the pilot study (CRYOSTAT1) it was shown that early replacement of fibrinogen with cryoprecipitate was able to rapidly restore fibrinogen levels (Figure B) and may reduce mortality from trauma haemorrhage [26]. 10% of all cryoprecipitate, which is the current standard source of concentrated fibrinogen in UK, is transfused to trauma patients [29] and no large study has evaluated the clinical importance of fibrinogen therapy.

Dose selection of intervention

The dose of fibrinogen concentrate for this study was chosen using results from *ex vivo* coagulation testing and CRYOSTAT1 data. CRYOSTAT1 used a 4g dose of fibrinogen (2 pools of cryoprecipitate) and results were suggestive of a beneficial clinical effect, without a safety risk. Clauss fibrinogen levels were maintained above 1.8g/L during active haemorrhage in patients in receipt of early cryoprecipitate (i.e. 4g fibrinogen). *Ex vivo* data, where increasing concentrations of either fibrinogen concentrate or cryoprecipitate were added to coagulopathic whole blood samples from trauma patients, showed an

incremental benefit of fibrinogen supplementation between 3g and 12g, dependent on dose of fibrinogen administered [6]. A 6g dose of fibrinogen, as cryoprecipitate or fibrinogen concentrate, resulted in significant increases in ROTEM clot strength values, suggestive of clinical efficacy.

The aim of this study is to evaluate 3 pools of cryoprecipitate (i.e. 6g fibrinogen) that will afford the most benefit to patients with the least associated risk. The CRYOSTAT1 study reported no thromboembolic events in the intervention arm and the average increase in Clauss fibrinogen level during active bleeding was 0.8g/L which is in-line with other studies [26]. When patients with major bleeding are treated with 4g fibrinogen supplementation, on average the blood fibrinogen level rises by 1g/L [30-32]. We have shown that trauma patients with major bleeding and ATC have fibrinogen levels of 1.6 g/L upon hospital admission [6]. Three pools of cryoprecipitate would be expected to increase the blood fibrinogen level by 1-1.5g/L and this would mean that the highest expected level of Clauss fibrinogen during active bleeding will be 3.0–3.5g/L; well within the normal range. This is not expected to be associated with an increase in thromboembolic disease.

Explanation for choice of comparators

This trial will evaluate the intervention: 3 pools of cryoprecipitate (15 units – 6g fibrinogen) IV, given as rapidly as possible, in addition to the standard major haemorrhage protocol.

The comparator will be the standard major haemorrhage protocol alone.

All participants in the intervention arm will receive 3 pools of cryoprecipitate (i.e. 15 units or 6g fibrinogen). This decision has been based on data from the CRYOSTAT trial, as well as prospectively collected fibrinogen blood levels in 517 trauma patients and previous patient data [30,31].

The early cryoprecipitate will be an additional treatment, over and above standard practice. Current standard practice for the management of trauma patients with severe bleeding is to use a major haemorrhage protocol (MHP) which enables rapid delivery and infusion of high ratio red blood cells and fresh frozen plasma.

For practical reasons, this trial is unblinded and is being conducted without a placebo comparator. The risks to the trial integrity is minimised given that the primary outcome of 28 day mortality is a hard endpoint.

Potential benefits and risks of Intervention

The potential benefits of the intervention are: an increase in blood levels of fibrinogen; improved haemostatic potential, reduction in bleeding and need for transfusion therapy and increased survival.

There are two main potential risks from the infusion of cryoprecipitate: a) thromboembolic disease and b) transfusion related adverse events which include transfusion transmitted infection and transfusion associated circulatory overload. These potential risks will be evaluated by the safety outcome data. The CRYOSTAT1 study administered 4g fibrinogen and found no venous or arterial thrombotic adverse events within the intervention arm and at 24 h and up to 28 days after randomisation the intervention group had fibrinogen levels that were no different to the comparator group. All participants entered into CRYOSTAT-2 will be expected to receive appropriate thromboprophylaxis (as per NICE guidelines [33]).

Study Objectives

This study will investigate the following:

- The effects of early fibrinogen supplementation in the form of 3 pools (15 units – 6g fibrinogen) of cryoprecipitate on 28-day mortality

Description of trial design

This is a randomised, unblinded, parallel group, controlled, multi-centre trial.

Study Setting

This study will be conducted in the Emergency Departments of participating Major Trauma Centres (MTCs) in the UK and at 1 Level 1 Trauma Centre in the USA.

Participating UK sites include:

Royal London Hospital, London
John Radcliffe Hospital, Oxford
Southampton Hospital, Southampton
St George's Hospital, London
St Mary's Hospital, London
Kings College Hospital, London
Derriford Hospital, Plymouth
Addenbrooke's Hospital, Cambridge
Southmead Hospital, Bristol
James Cook University Hospital, Middlesbrough
Leeds General Infirmary, Leeds
Queen's Medical Centre, Nottingham
Royal Victoria Infirmary, Newcastle
Hull Royal Infirmary, Hull
Northern General Hospital, Sheffield
Queen Elizabeth Hospital, Birmingham
Royal Preston Hospital, Preston
University Hospital, Coventry
University Hospital of North Staffordshire, Stoke on Trent
Manchester Royal Infirmary, Manchester
Royal Salford Hospital, Salford
Aintree University Hospital, Liverpool
University Hospital of Wales, Cardiff
Royal Victoria Hospital, Belfast

Participating site in the USA:

University of Texas Health Science Center

Selection of Sites/Clinicians

In the UK, all adult MTCs will be included in this study.

For other sites, selection will be based on the presence of appropriate clinical and research infrastructure including adequate local resources and facilities to support recruitment, and adequate qualified staff to conduct the trial properly and safely.
The site selection process will include an evaluation of the site's potential rate of accrual to the trial, which will review the types of patient treated, an assessment of how many patients would be eligible, and how many patients may be recruited given the site level resource. Site selection will include a review of any barriers to recruitment such as other trials recruiting from the same patient population.

The trial sponsor has overall responsibility for site and Investigator selection.

Site/Investigator Inclusion Criteria

To participate in the CRYOSTAT-2 trial, investigators and clinical trial sites must either be a UK MTC or fulfil a set of basic criteria that have been prepared by the CRYOSTAT-2 Trial Management Group (TMG) and are defined below.

The clinical trial sites should:

A) Be designated a Level 1 trauma centre and/or admit > 50 adult trauma patients per year who require activation of the major haemorrhage protocol in Emergency Departments (ED)

B) Have an established research infrastructure in ED, enabling recruitment of actively bleeding trauma patients

C) Have a defined Major Haemorrhage Protocol (MHP)

3.2 PI Qualifications and Agreements

The investigator should be qualified by education, training and experience to assume responsibility for the proper conduct of the trial at their site and should provide evidence of such qualifications through an up to date curriculum vitae and/or other relevant documentation requested by the Sponsor, the REC, and/or the regulatory authorities.

Selection of Participants

Adult trauma patients will be identified as follows: (1) at scene by the Air Ambulance team who will notify the receiving hospital; (2) by the trauma team leader on arrival of the patient at the emergency department or (3) by the research team personnel following a trauma call activation. Patients will be assessed for eligibility to enter the trial according to the criteria set out below.

If patients are eligible for entry into the study following initial screening, they will be enrolled automatically under a waiver of consent.

Participant Inclusion Criteria

Patients are eligible for this trial if:

1. The participant is judged to be an adult (according to local practice, e.g. 16 years or older in UK) and has sustained severe traumatic injury

2. The participant is deemed by the attending clinician to have on-going active haemorrhage

AND REQUIRES:

3. Activation of the local major haemorrhage protocol for management of severe blood loss

AND HAS STARTED or HAS RECEIVED:

4. at least one unit of any blood component

Participant Exclusion Criteria

A patient will not be eligible for this trial if he/she fulfils one or more of the following criteria:

1. The participant has been transferred from another hospital

2. The trauma team leader deems the injuries incompatible with life*

3. More than 3 hours have elapsed from the time of injury (taken as time of the 999 call if unknown by medical team).

* Incompatible with life: While some situations are objective, such as decapitation, others will remain in the experienced, but subjective opinion of the physician. These include catastrophic brain injury, severe truncal injuries, and a constellation of injuries that results in the patient being declared dead on arrival (DOA) or that will likely result in death within 30 minutes of arrival, regardless of resuscitative efforts. Further examples of patients inappropriate for the trial include: (1) Moribund patient- expected to die within one hour of ED admission (per trauma team attending); (2) Severe traumatic brain injury patients in which further care has been deemed “futile” by neurosurgical examination and evaluation of CT findings; (3) Received greater than five minutes of cardiopulmonary resuscitation (CPR) in the pre-arrival or ED setting; (4) Patients with concomitant burns greater than 20% total body surface area (TBSA) burns or documented inhalation injury.

Patients who object to a blood transfusion

Patients who object to a blood transfusion will not be eligible for this study. As part of the eligibility criteria assessment, patients will be excluded if they have not received at least one unit of any blood component. This criterion will therefore exclude patients who refuse a blood transfusion.

In the UK: Patients who are known Jehovah's witnesses or with an advanced directive refusing blood transfusion will not be eligible for this study.

In the USA: As part of the rigorous community consultation process we will specifically approach those in communities that have noted objections to blood transfusion for religious reasons and consult with them directly. In addition to medic-alert bracelets or other IDs that they may already carry, we will offer them other identifiers of "opt-out" such as bracelets, free of charge. This will be in addition to local practice at the participating institution who will already be practicing their standards of care for identifying those with medic-alert bracelets and other identifiers.

Patients will be considered eligible for enrolment in this trial if they fulfil all of the inclusion criteria and none of the exclusion criteria detailed above.

Co-Enrolment Guidelines

See Section 6.6 "Co-enrolment Guidelines"

Screening Procedures and Pre-randomisation Investigations

1. The local trauma team (or in some centres the research team) will be responsible for identifying suitable participants
2. The eligibility checklist will be completed.
3. A screening log will be completed (see section 5.1.1).

Consent

Consent Procedures

Consent Procedures England, Wales and Northern Ireland

The consent procedures described below apply to sites in England, Wales and Northern Ireland.

This study seeks to include participants who have been affected by injury that has resulted in uncontrolled bleeding. These participants will be incapacitated at the time of screening for this study for a variety of reasons including the circumstances of the traumatic event, the nature of their injuries, being in severe pain, being under anaesthesia, having reduced consciousness, and/or the use of strong analgesia. Furthermore, sudden traumatic injury cannot be predicted or foreseen, and there is no opportunity to seek consent in advance. The participants will therefore be incapable of giving consent prior to enrolment in the study.

Severe trauma haemorrhage is an emergency condition and any treatment needs to be given as soon as possible. The need for urgent treatment in this study means that the implementation of the research cannot be delayed until advice can be obtained from a professional or personal consultee. As injury is an unexpected event, it is uncommon that relatives are present at the time of arrival at hospital, and they too are unable to go through the consultee process in the timeframe required of the intervention. Participants who are incapable of giving consent in emergency situations are an established exception to the general rule of informed consent in clinical trials. This is acknowledged in the Declaration of Helsinki, 2013:

'*Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research study should be obtained as soon as possible from the subject or a legally authorised representative.'*

The following procedure, which is in accordance with the Declaration of Helsinki, 2013, will be used for giving information and enrolling participants in England, Wales and Northern Ireland into the CRYOSTAT-2 study.

Study entry

All participants will be enrolled in the study without informed participant consent due to the emergency nature of the trial (i.e. a "waiver of consent" will be applied). The participant will then be randomised and the allocated intervention will be delivered within ninety minutes. This may be before the participant regains capacity or there is any opportunity to identify and approach a personal consultee. As a result, consent can only be sought for the participant to remain in the study through the ongoing collection of follow-up data, and "retrospective consent" for the administration of cryoprecipitate is not possible. As soon as

appropriate after the administration of the intervention, a personal consultee for the participant will be identified and approached, given an information sheet and asked to provide their advice for the participant to remain in the trial. If the participant remains incapacitated and a personal consultee is not available, or if approaching the personal consultee is likely to induce a delay or it is deemed by the research team to be inappropriate to approach the personal consultee, advice from a professional consultee will be sought.

For the purpose of this study, a professional consultee is defined as a clinician (qualified doctor or registered nurse) with appropriate training (according to local Trust policies) to take on the role of professional consultee. Professional consultees must not be directly involved in the patient's care and cannot be a member of the core research team at site. Professional consultees should be aware of the aims of the study and know what the intervention is.

Sites should obtain the advice of a professional consultee as soon as possible after randomisation to enable continued collection of data should the patient be discharged/self-discharge/transferred to another NHS Trust before the research team can approach the patient and/or personal consultees for consent/advice.

The research team will monitor the ongoing status of the participant and their ability to provide informed consent. If the participant does not regain capacity, a personal and/or professional consultee's advice is sufficient for the participant to remain in the study for the ongoing collection of follow-up data at site up to day 28, discharge or death.

Information giving and written informed consent in England, Wales and Northern Ireland

When a participant regains capacity to give consent, full information will be provided to them and they will be asked to sign a consent form agreeing to their continuation in the study. It will be explained to the participant that they have already received the study treatment.

If a patient is discharged/self-discharges or is transferred to another NHS Trust before consent is obtained, researchers should contact the participant at home to complete the consent process. Up to three attempts to contact participants at home are permitted (a combination of telephone calls and letters at the researchers' discretion). In some situations, it may not be possible for the research team to locate or contact the participant post discharge, and in such circumstances, section 251 approval will be sought via the Confidentiality Advisory Group to permit continued data collection from NHS Digital and TARN (see section 9).

For any participant who is enrolled but does not regain capacity up to study day 28/discharge, or who did not have capacity prior to being injured, the opinion of a personal consultee will be sought, under the provisions of the Mental Capacity Act, at the earliest opportunity and no later than the day 28 follow-up point.

In the event that a participant dies during their hospital stay, an opinion regarding the participant's likely wishes may already have been sought from a personal consultee as described above. In some situations, where a participant's death occurs soon after hospital arrival, there may have been no opportunity for contact between the research team and the personal consultee prior to the participant's death. In this instance, we recognise that

approaching a personal consultee to ask their opinion is likely to be distressing and without benefit. Families of bereaved participants should not be contacted by the research team after participant death to obtain personal consultee advice. In these cases, advice from a professional consultee should be sought so that data collection can be completed at site.

In this circumstance the local clinician in charge of the participant's care will access and anonymise the data to be provided to the study teams. These procedures will be conducted in accordance with the Access to Health Records Act 1990. Although we will not approach a personal consultee to seek their opinion when a participant dies before any contact has been made with the research team, in all other cases we will make every effort to inform relatives that the participant was entered into the trial.

In the rare event that a participant is found to be below 16 years of age after the point of entry, consent will be obtained from the participant's Parent/Guardian and assent will be sought from the child if and when sufficiently recovered. This will be evidenced by parental/guardian signature on the personal consultee form.

There are circumstances whereby obtaining a personal consultee declaration and/or patient signed informed consent due to COVID-19 restrictions in hospitals are not practicable. An example of this would be if a participant is on a COVID-19 ward with no visitors or staff visits allowed.

The use of the PANDO Application (https://hellopando.com/nhs/) for the electronic transfer of patient signed informed consent forms from COVID-19 restricted wards to the site research team is encouraged.

Initial verbal consent can be taken from COVID-19 positive individuals or those in restricted wards in hospital if it is documented appropriately in the medical notes and NHSBT CTU is informed via a file note. When it is safe to do so, the participant can be approached for an informed consent form signature. If the participant has been discharged, the participant can be contacted and consent can be obtained electronically. Research staff must verify the identity of the participant and undertake a real-time discussion about the study with a view to informed consent. Following this, the consent form can be emailed to the participant, who can either sign electronically and return the form, or print and physically sign the form and return it by post.

Personal Consultees can be contacted at home with a view to signing and returning a consultee declaration if a potential consultee is known to the direct care team (e.g. life partner, sibling, parent) and contacting the consultee is unlikely to cause later distress to the participant. The personal consultee can be contacted at home and a consultee declaration can be obtained electronically. Research staff must verify the identity of the personal consultee and undertake a real-time discussion about the study with a view to an informed consultee declaration. Following this, the personal consultee form can be emailed to the consultee, who can either sign electronically and return the form, or print and physically sign the form and return it by post.

A participant or their consultee is free to withdraw their consent or change their opinion regarding continuation in the trial at any time without penalty, loss of benefits or alterations to the care which they receive. Participants can withdraw with or without permission for follow-up data collection. If participants withdraw and do not provide permission for continued data collection, data collected up to the point of withdrawal will be retained for

continued data collection. Although the participant is not required to give a reason for withdrawing consent, a reasonable effort will be made to establish this reason while fully respecting the participant's rights.

The requirements of the relevant ethics committee will be adhered to at all times.

Consent procedures for US sites

Participants enrolled at international sites will be subject to the regional or national ethical code of practice for conducting research in incapacitated adults and this may include waiver of consent procedures e.g. "Exception From Informed Consent" (USA).

Screening Log

A screening log will be completed once a week at each site which will record all patients considered for eligibility for enrolment in the trial. The log will include age, sex, inclusion/exclusion criteria and other reasons for non-enrolment. The screening log data will be reviewed at regular intervals by the CTU.

The local principal investigator and research nurse will be responsible for completing the screening log after an eligible patient has been identified and considered for participation in the trial.

Randomisation

Allocation – sequence generation

The allocation sequence will be produced by the trial statistician using SAS statistical software. The allocation sequence will have a varying block size that will not be disclosed, and will be stratified by centre.

Participants will be allocated to a 1:1 ratio intervention (early cryoprecipitate) vs. comparator (standard MHP) arm.
See Section 10.

Allocation – concealment mechanism

Allocation cards will be prepared, which will be contained within sequentially numbered opaque sealed envelopes, independently and in advance by the CTU and provided to participating sites. Each envelope will contain a randomisation number and the allocated treatment. Envelopes will be opened in sequential order.

These envelopes will be tested for 100% concealment and closed with a tamper-proof seal, preventing opening and resealing. Envelopes will be securely stored in a locked cupboard at each site, access to which is controlled by the research team. Envelopes will be sequentially released by the CTU in small batches sufficient to support projected recruitment and replace used envelopes.

Allocation – implementation

Randomisation can take place in the Emergency Department or the Transfusion Laboratory/Blood Bank.

Members of clinical teams, research teams and transfusion teams will enrol participants and assign them to the randomised treatment.

Participant allocation will be made by selecting the next pre-sealed randomisation envelope in sequence at each site. The number on the envelope will be checked against an enrolment log to ensure that the correct envelope has been selected.

The recruiting staff will complete the enrolment log each time an envelope is taken for use and will sign and date the envelope across the unbroken seal to confirm that the next available and lowest numbered envelope of the batch has been taken, that it is unopened and bears no evidence of tampering.

The participant's initials, date of birth and hospital number will also be written on the envelope prior to opening. (If initials and date of birth are not known, document the unique identifiers used at your participating hospital for identifying unknown patients). Correct and sequential use of envelopes will be strictly audited by the site research team and CTU trial coordinator at site monitoring visits.

If the randomised intervention differs from that the participant received, a reason for this will be requested. These processes will allow for clear and regular auditing of the randomisation process through comparison with the randomisation list held by the statistician.

Defrosted cryoprecipitate for early administration will be supplied to the ED by the site's blood bank/transfusion laboratory. This is an unblinded trial and as soon as the cryoprecipitate reaches the participant's bedside it will be administered.

The cryoprecipitate that is used for study purposes (rather than for standard major haemorrhage therapy) will be specifically labelled as CRYOSTAT-2 cryoprecipitate to facilitate tracking for study purposes and to distinguish the intervention from cryoprecipitate given as part of the standard major haemorrhage protocol. This can be achieved by use of the yellow study bags provided by NHSBT CTU or by locally designed labels.

Randomisation Practicalities

Eligibility for enrolment will be assessed with reference to the specific inclusion and exclusion criteria, described in Sections 4.1 and 4.2

The local PI/delegate is responsible for informing the participant's General Practitioner (GP) of the patient's participation in the trial, and for placing a label indicating trial participation in the participant's medical notes or annotating their electronic notes appropriately.

The cryoprecipitate for early administration in the trial will be stored in the blood bank/transfusion laboratory in keeping with national guidelines for the storage and administration of blood products.

The PI or delegate must update the site screening log by adding randomisation numbers for all participants randomised.

Randomisation Codes

The participant ID (randomisation) number consists of a 6 character number, the first character denoting **R** and the remaining 5 digits the unique participant number from 00001 to 99999 e.g. R00001.

Co-enrolment Guidelines

Participation in any other type of intervention trial will be considered for each individual trial and must be approved by the Trial Management Group or Co-Investigator.

Blinding

This is an unblinded trial. The risks to the trial integrity is minimised given that the primary outcome of 28 day mortality is a hard endpoint.

Treatment of Participants

Introduction

Participants will be randomised 1:1 to either the intervention (early cryoprecipitate) or comparator (standard MHP) arm.

The early cryoprecipitate will be started as per randomisation as soon as possible and within 90mins after arrival in ED.

The participant's eligibility criteria MUST be confirmed to ensure they are still eligible prior to administration of the trial product.

The cryoprecipitate for early administration will be stored and defrosted in the blood bank/transfusion laboratory at the participating hospital and sent to the Emergency department on request.

Interventions

Intervention to be studied

Early cryoprecipitate – 3 pools (equivalent to 15 single units cryoprecipitate or 6g fibrinogen supplementation), infused as rapidly as possible, within 90 minutes of arrival at hospital.

IN ADDITION to standard major haemorrhage protocol

Comparator

Standard major haemorrhage protocol only

Standard major haemorrhage protocol

Standard treatment of major traumatic haemorrhage involves administering red blood cells, fresh frozen plasma and platelets following a major haemorrhage protocol (MHP).

Each participating site will follow their local standardised MHP which will broadly align with the current accepted best practice for transfusion therapy i.e. Damage Control Resuscitation, and which will include:

High ratio empiric delivery of RBC, FFP and platelets in a balanced resuscitation.

The recent PROPPR randomised clinical trial reported that there was no difference in overall survival between early administration of plasma, platelets and red blood cells in a 1:1:1 ratio compared to 1:1:2. However more patients in the 1:1:1 group achieved 'anatomic' haemostasis and fewer experienced death due to exsanguination by 24 hours [11]. The MHP will comprise a balanced resuscitation with blood products and will be standardised as much as possible across participating sites, however some degree of variation is inevitable and pragmatic, reflecting actual clinical practice. Furthermore, the transfusion products given may vary to some extent from the target ratio according to blood product availability and the participant's ongoing clinical condition.

Preparation of Intervention

Early cryoprecipitate (3 pools = 6g fibrinogen) will be stored in its frozen state and will be defrosted according to the local standard operating procedures for each blood bank/transfusion laboratory at participating sites. In UK these procedures will be in accordance with the 'red book' transfusion guidelines [34].

Cryoprecipitate can be defrosted within 15-20 minutes and will be made available as quickly as possible. The bags of cryoprecipitate for early administration will be labelled with a trial specific label in order to differentiate trial cryoprecipitate from any cryoprecipitate given as standard of care.

As an alternative and depending on approval for use, pre thawed cryoprecipitate may also be used during the trial.

Administration of Intervention

The early cryoprecipitate will be started as soon as possible and within 90 minutes of participant arrival at hospital and enrolment.

The 3 pools (15 units) of cryoprecipitate will be administered as rapidly as possible via an intravenous line and in accordance with local practice.

The cryoprecipitate must not be mixed with platelets prior to infusion.

Concomitant Medications

There are no restrictions on treatments that can/cannot be given during this trial as long as the treatments are part of standard care and are not administered as part of another trial (unless authorised by the TMG or delegated Co-Investigator).

Transfusions not permitted

None

Medications not permitted

None

Study Outcomes

Please also refer to the section on sample size for a discussion about outcomes.

Primary Outcome Measure

All-cause mortality at 28 days

Secondary Outcome Measures

All-cause mortality (including death from bleeding) at 6 hours, 24 hours, 6 months and 12 months from admission

Death from bleeding at 6 hours and 24 hours

Transfusion requirements, in numbers of units, for RBC, platelets, FFP & cryoprecipitate at 24 hours from admission, including pre-hospital transfusion

Destination of participant at time of discharge from hospital

Quality of life measures: EQ5D-5L and Glasgow Outcome Score at discharge/day 28 and 6 months after injury

Hospital resource use up to discharge or day 28, including ventilator days, hours spent in critical care and in-patient stays

Safety Outcome Measures

Symptomatic thrombotic events: venous thromboembolism (DVT, PE) and arterial thrombotic events (eg MI, stroke) from randomisation up to day 28 or discharge from hospital.

Assessments and Follow-up

Trial Assessment Schedule

*Timepoint**	*On arrival at hospital*	*Enrolment*	*Post randomisation*					
		T_0	T_1	T_2	T_3	T_4	T_5	T_6
ENROLMENT								
Eligibility Screen		*X*						
Emergency waiver		*X*						
Randomisation/allocation		*X*						
INTERVENTION			↔					
Cryoprecipitate (3 pools, 15 units) in addition to MHP			*X*					
Major haemorrhage protocol (MHP) alone			*X*					
ASSESSMENTS								
Participant characteristics		*X*						
Clinical assessment		*X*						
TXA administration			*X*					
RBC, FFP, cryo, platelets (including given pre-hospital)	*X*				*X*			
Mortality			*X*	*X*	*X*	*X*	*X*	*X*
Serious Adverse Events					*X*	*X*		
Participant destination at discharge						*X*		
Glasgow Outcome Score						*X*	*X*	
EQ5D-5L						*X*	*X*	
**Timepoints are:*	*T_o – Enrolment & allocation of early cryoprecipitate, must be within 90 minutes of arrival at hospital* *T_1 – cryoprecipitate administered, must be started within 90 minutes of arrival at hospital* *T_2 – 6 h (± 1 h) from arrival at hospital* *T_3 - 24h (± 4 h) from arrival at hospital* *T_4 – date of discharge or day 28 (± 4 days) from arrival at hospital whichever is the sooner* *T_5 - 6 months (± 14 days)* *T_6- ≥12 months (mortality data post discharge to be captured by flagging with the ONS)*							

Procedures for Assessing Efficacy

Data collection will be the responsibility of the local clinical team led by the local PI and research personnel at each site. Data will be recorded on paper CRFs which will be compiled by the CTU. Three participant identifiers (Participant ID allocated at enrolment, initials and site) will be captured on the CRF.

Assessments will be performed according to the schedule in Section 9.1. Overall responsibility for collating data from all centres will reside with the Trial Manager. CRF data will be anonymised with participants assigned a unique participant ID number at enrolment. A copy of consent and withdrawal forms will be filed in the participant's hospital

notes, investigator site file and a copy will be given to the participant and participant representative (as appropriate). Completed consent forms will not be sent to the CTU. The procedure for SAE reporting is detailed in Section 10.

Screening Procedures

It will be the responsibility of the local trauma teams or the local researcher(s) to identify eligible adult trauma patients with active bleeding who activate the local major haemorrhage protocol. Assessment of inclusion/exclusion criteria will be performed at screening. Once final eligibility is confirmed and agreement for study entry is obtained, the adult trauma patient will be enrolled into the study.

The screening log will be completed as set out in section 5.1.1.

Enrolment Procedures

Enrolment will occur as soon as possible after screening and agreement for entry (or waiver) into the study has been gained. Background data (participant characteristics) will be collected and include; mechanism of injury, injury type and severity, participant age and sex.

Clinical data will also be collected, and this will include: vital signs (SBP, HR, and GCS) at the first hospital measurement. Data will also be collected on blood product infusions given to the participants including all red blood cells and other blood component therapy. The injury severity score will be collected retrospectively by the central study team from TARN.

At the time of enrolment, the following procedures will be completed:

- Documentation of arrival time (as identified in the ED trauma notes or 999 call time)
- Documentation of numbers of units of RBC, FFP, platelets, cryoprecipitate, whole blood (red cells and plasma in one unit), given from injury to arrival at the ED

Procedures at the time of early cryoprecipitate administration

The start time will be recorded. The time recorded will be the start time for the first of the three pools (15 units) of early cryoprecipitate.

If there is a delay in cryoprecipitate infusion (i.e. the start of the infusion is >90 minutes from arrival at hospital), study personnel must document the reason(s) that have led to protocol deviation.

It is still permissible to start the early cryoprecipitate infusion up to 3 hours from the time of injury. If more than 3 hours from injury have elapsed the study cryoprecipitate must not be started. If it is discovered retrospectively that participants were enrolled more than 3 hours from injury, study personnel must document the reason(s) that led to protocol deviation.

Procedures at 6 hours after arrival at hospital

Data collection will be undertaken at 6 hours ± 1 hour after arrival at hospital.

The following procedures will be undertaken:

- Mortality at 6 hours

- Documentation of adverse events (including SAEs)

Procedures at 24 hours after arrival at hospital

Data collection will be undertaken at 24 hours ± 4 hours after arrival at hospital.

The following procedures will be undertaken:

- Recording of numbers of all RBC and other blood components administered from arrival at hospital to 24 hours
- Administration of TXA
- Mortality at 24 hours
- Documentation of adverse events (including SAEs)

Procedures for day 28 follow up or day of discharge

At day 28 (± 4 days) or day of discharge (whichever is the sooner) the following data will be collected:

- Length of stay in hospital including length of stay in ICU or HDU (times and dates when a participant is transferred to ICU/HDU and from ICU/HDU to the ward will be collected)
- Ventilator days
- Thromboembolic adverse events (see below for definitions)
-
- Thromboprophylaxis measures
- Documentation of serious adverse events
- Date of discharge and destination of participant i.e. home, transfer to another hospital
- Glasgow Outcome Score *(see section 9.3)*
- EQ5D-5L *(see section 9.3)*
- Documentation of mortality (*ONLY* if data collection falls within 24 – 32 days of study entry i.e. day 28 (± 4 days))

Procedures for day 28 follow up

At day 28 (± 4 days) the following data will be collected:

- Documentation of mortality

If a participant has been discharged prior to day 28 (±4 days) – centralised mortality data will be captured via the Office for National Statistics (ONS).

Patients' health records enrolled at MTCs in England will be flagged for death up to 1 year from date of admission via a data access agreement with NHS Digital (who hold the mortality data on behalf of ONS). Flagging data (including patient name, NHS or CHI number, date of birth, sex and postcode) will be submitted to NHS Digital on a periodic basis for the receipt of mortality data including date and cause of death (if applicable). Flagging data will be stored on password protected secure NHS servers and access restricted to appropriate members of the research team. Patients will be asked to consent to their identifiable data being shared for this purpose. Patient confidentiality will be maintained by use of a unique trial identifier and only sex, age and initials will be captured

on the study database. NHSBT and QMUL will carefully manage this process, in accordance with GDPR and the necessary permissions from NHS Digital/CAG.

In the unlikely event that mortality data are not available, or a patient is considered lost to follow up, the research team at the study centre will be asked to contact the patient's GP to confirm their survival status, and if appropriate, contact the patient. Patients will be fully informed of this mechanism and asked to consent to being contacted in such circumstances via written informed consent.

1.1.1 Procedures for follow up post discharge in the event that written informed consent is not obtained

In some cases, it is not possible to obtain written informed consent from participants.

Examples include:

- Unexpected discharge (e.g. overnight or weekends)
- Unexpected self-discharge (including absconding from authorities)
- Participants who are rapidly discharged to police custody or returned to the custody of HM Prison Service
- Participants who are rapidly transferred to mental health trusts under section
- Participants who have been repatriated to a non-participating hospital or residential nursing care home or rehabilitation centre
- Participants who provide false details or refuse to give any details to hospital staff
- Participants who are homeless with no listed general practitioner
- Participants in hospital who are abusive, aggressive or violent and the research team have been advised not to approach the patient
- Participants in hospital who are abusive, aggressive or violent and the research team have been advised not to approach the patient
- Participants who have considerable language difficulties where it has not been possible to provide an NHS translator or ask a family member to translate information about the trial

In England and Wales: During admission, every attempt will be made by the research team to consent participants once capacity has been restored. In the event that informed consent is not obtained prior to discharge, irrespective of whether a participant has a personal or professional consultee, permission will be sought from the Confidentiality Advisory Group (CAG) under Section 251 approval to collect and transfer patient identifiable data (patient name, NHS or CHI number, date of birth, sex, postcode and date of arrival at hospital) to TARN and NHS Digital in order to capture injury severity score,, quality of life data at hospital discharge and 6 months post-admission and mortality status up to 1-year post-admission.

In Northern Ireland:
During admission, every attempt will be made by the research team to consent participants once capacity has been restored. In the event that informed consent is not obtained prior to discharge or after three attempts to contact the patient, follow-up data cannot be collected.

Procedures in the event of death

If a recruited participant dies during the first 28 day period, the following information will be documented:

- Date and time of death
- Primary cause of death will be documented and if possible categorised according to the following clinical causes:
    - uncontrolled bleeding; vascular occlusion (myocardial infarction, stroke); pulmonary embolism; multi-organ failure; traumatic brain injury; multiple injury; sepsis; other (reason).

Procedures for Assessing Quality of Life (all sites in England and international sites depending on resource) at day 28 follow up or day of discharge and 6 months

PROMs (Patient Reported Outcome Measures) questionnaires including the EQ5D-5L and the Glasgow Outcome Scale (GOS) are routinely collected from eligible patients at all major trauma centres across the UK as part of an ongoing TARN PROMs Project. CRYOSTAT-2 will use this ongoing initiative to collect PROMs questionnaires at two timepoints for all enrolled patients – (a) during first hospital admission (by research team) and (b) at 6 months from injury by TARN (±14 days). The Glasgow Outcome Scale during first hospital admission is not collected routinely as PROMS data and therefore will be collected by the local research team for CRYOSTAT-2.

The PROMs data (EQ5D-5L) will be collected by the research team during first hospital admission at study day 28 or at hospital discharge. Each hospital in UK participating in CRYOSTAT-2 should have an agreed local policy for the completion of PROMs questionnaires on behalf of those participants who do not regain mental capacity during admission either by patient representative or Investigator as appropriate. If quality of life data at discharge has not been collected by the research teams in hospital, data collected by TARN in the PROMs questionnaires will be provided by TARN,

TARN eligible participants will be contacted by TARN at 6 months from the time of injury (± 14 days) by letter to complete the EQ5D-5L and GOS questionnaires (as well as additional PROM questionnaire data). This is a routine part of the TARN PROMs project. The questionnaires may be completed on paper or via an on-line questionnaire. Standard checks will be undertaken to check the participant is alive prior to contact. For the purposes of this study, those participants competent to consent to the study during their hospital stay, and who remain alive, will be assumed to have capacity at 6 months.

For participants entered into CRYOSTAT-2 who provide PROMs data, the same patient identifiers collected for NHS Digital mortality data (participant name, NHS or CHI number, Questionnaire Identification number (QID), date of birth, sex postcode and date of arrival at hospital) will be submitted to TARN to enable data transfer between TARN and the NHSBT CTU. Patients will be asked to consent to their identifiable data being shared for this purpose.

In England and Wales: For participants where it has not been possible to obtain written informed consent and the patient was alive on discharge, Quality of Life data at discharge and 6 months post-admission will be obtained from TARN under Section 251 approval.

In NI: For participants where it has not been possible to obtain written informed consent and the patient was alive on discharge, attempts will be made to contact the patient with a view to informed consent. If informed consent is not obtained, Quality of Life data at hospital discharge and 6 months cannot be collected from TARN.

Procedures for Assessing Safety

Safety outcomes will be assessed for all participants until day 28 (or death) or until discharge from the acute medical facility (whichever is the sooner). Each safety outcome will be recorded and the presence or absence of each safety outcome will be reported.

The following outcomes will be assessed:

a) Symptomatic venous thrombotic events
   - Pulmonary embolus
   - Deep venous thrombosis (of the limbs or other significant veins i.e. portal vein)

b) Symptomatic arterial thrombotic events
   - Myocardial infarction
   - Ischaemic stroke
   - Other (occlusion of any other artery)

For a VTE to be diagnosed and reported in this trial there must be clinical symptoms and definitive radiological evidence as set out in the table below:

Type of venous thromboembolism	**Diagnosis**
Deep venous thrombosis	Accepted methods of diagnosis include: • compression ultrasound • venography • CT scan/MR venogram if more proximal leg veins or abdominal veins involved
Pulmonary embolism	Accepted methods of diagnosis include: • CT – pulmonary angiogram (CTPA) • Ventilation-Perfusion scan (V/Q or Q scan as per local guidelines) • SPECT scan

Definitions of ischaemic events:

Type of ischaemic event	**Diagnosis**
Myocardial infarction	The term myocardial infarction (MI) should be used when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischaemia. Under these conditions presence of one of the following criteria meets the diagnosis of MI: • Detection of rise of troponin with at least one value above the 99th percentile of the ULN, plus evidence of myocardial ischaemia with at least 1 of the following: o symptoms of ischaemia o ECG changes indicative of new ischaemia [ST-T changes, or LBBB] o development of pathological Q waves in ECG o imaging evidence of new loss of viable myocardium or new regional wall motion

	abnormality • Sudden, unexpected cardiac death, often with cardiac symptoms, and accompanied by new ECG changes, but before blood tests could be taken or death occurred before the appearance of cardiac biomarkers in the blood • Pathological findings of acute MI
Ischaemic stroke	Clinical report of brain imaging consistent with an ischaemic stroke in association with new onset focal or generalised neurological deficit (defined as deficit in motor, sensory or co-ordination function).

(The definition for MI is taken from a consensus document published on behalf of the Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction, 2007).

Transfusion related serious adverse events will be documented, as defined by SHOT.

Other Assessments

Hospital resource use up to discharge or day 28 (whichever is the sooner) will be calculated from information provided as part of the study CRF, and will be detailed in the trial analysis plan.

Participant transfers

If a participant is transferred to another participating hospital (MTC), responsibility for ongoing data collection and safety reporting is transferred to the research team at the receiving hospital.

If a participant is transferred to non-participating hospital or moves from the area after discharge from the acute facility, every effort will be made to maintain contact to allow the follow-up study procedures to be completed. This will be the responsibility of the participating site.

Loss to Follow-Up

Loss to follow-up in England and Wales

A participant will be considered lost to follow-up for the primary endpoint (28 day mortality) if the participant has been discharged from hospital prior to day 28; has no data reported via the NHS Digital reporting system; and the research team is unable to confirm their survival status with their GP or unable to contact the participant by telephone.

A participant will be considered lost to follow-up for the 6 month data collection if they do not respond to two attempts by TARN to contact them for the 6 month quality of life assessment.

Loss to follow-up in Northern Ireland

A participant will be considered lost to follow-up for the primary endpoint (28 day mortality) if the participant has been discharged from hospital prior to day 28; no mortality data can reported by the research team from participating Trust records or the research team is unable to confirm their survival status with their GP or unable to contact the participant by telephone.

A participant will be considered lost to follow-up for the 6 month data collection if they do not respond to two attempts by TARN to contact them for the 6 month quality of life assessment.

Loss to follow-up in the US
A participant will be considered lost to follow-up for the primary endpoint (28 day mortality) if the participant has been discharged from hospital prior to day 28; no mortality data can reported by the research team or the research team is unable to confirm their survival status.

Trial Closure

The trial will be considered closed when all surviving participants have completed the 6 month follow up, been deemed lost to follow-up or withdrawn, and all the data have been cleaned and the database locked. At this point, the participating sites will be contacted and visited to ensure that the documentation for study closure is complete and archived appropriately.

Safety Reporting

The principles of ICH GCP require that both investigators and sponsors follow specific procedures when notifying and reporting adverse events or reactions in clinical trials. These procedures are described in this section.

Definitions of Adverse Events

The definitions to be applied to adverse events recorded in this trial are given in Table 1a below. As this is a trial using cryoprecipitate, events of interest are those related to major trauma haemorrhage and cryoprecipitate transfusion, which are also study outcomes.

Table 1a: Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant or clinical trial subject to whom a blood component has been administered.
Transfusion Related Adverse Reaction or Event	Any untoward and unintended response to a transfused blood component.
Serious Adverse Event (SAE) or Serious Transfusion related Adverse Reaction	Respectively any adverse event, adverse transfusion reaction or unexpected adverse transfusion reaction that: results in death is life-threatening* requires hospitalisation or prolongation of existing hospitalisation** results in persistent or significant disability or incapacity
Unexpected Adverse Transfusion Reaction	An adverse reaction, the nature or severity of which is not consistent with the known reactions to transfusion of a blood component (in the case of this trial, cryoprecipitate).

*The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

**Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition (including elective procedures that have not worsened) do not constitute an SAE.

Expected Serious Adverse Events

Participants in this study have suffered traumatic injury and by definition will have multiple serious adverse events during their admission. In this study serious adverse events relating to the nature of their traumatic injuries will not be recorded apart from:

- Death (cause of death will be documented and if possible categorised according to the following clinical causes: uncontrolled bleeding; vascular occlusion (myocardial infarction, stroke); pulmonary embolism; multi-organ failure; traumatic brain injury; multiple injury; sepsis; other (reason).
- Thromboembolic events (including Pulmonary embolus, Deep venous thrombosis (of the limbs or other significant veins i.e. portal vein), Myocardial infarction, Ischaemic stroke, Peripheral ischaemia causing tissue loss and other occlusion of any other artery)
- Serious transfusion related adverse reactions which relate to the administration of the cryoprecipitate transfusion (definitions of these will in accordance with SHOT/SABRE guidelines).

Any other adverse or serious adverse event not listed above will not require reporting.

Investigator Responsibilities

The Chief Investigator (CI) has overall responsibility for the conduct of the study. As this is a multi-site study, the Principal Investigator (PI) has responsibility for the research at their local site and is responsible for informing the CTU of all SAEs occur at their site following the guidelines below.

Investigator Assessment of SAEs

The Principal Investigator is required to consider seriousness, causality and expectedness of any SAE. Causality will be assessed according to the following categories:

Table 7b: Definitions of Causality

Relationship	Description
Unrelated	There is no evidence of any causal relationship
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial transfusion). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).
Possible	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial transfusion). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).
Probable	The evidence is clearly in favour of attributing the adverse reaction to the blood or blood component.
Definitely	There is conclusive evidence beyond reasonable doubt attributing the adverse reaction to the blood or blood component.

Investigator Notification

- The CTU should be notified within 24 hours of the investigator becoming aware of a SAE. Investigators should notify the CTU of all SAEs occurring during the study period.
- The SAE form must be completed by the Investigator (the consultant named on the delegation of responsibilities log who is responsible for the participant's care). In the absence of the Investigator, the form should be completed and signed by a member of the site trial team and emailed to NHSBT CTU. The responsible Investigator should subsequently check, annotate and sign the form and re-fax/email to the CTU as soon as possible. The initial report must be followed by detailed written reports as appropriate.
- The investigator must follow-up all reported SAE's until resolution or the event is considered stable.
- Investigators must supply the CTU, REC and relevant NHS Trust R&D with any supplementary information they request.

Sponsor's Responsibilities (QMUL with NHSBT CTU delegated responsibility)

- The CTU will forward all reported serious adverse events received to the Chief Investigator (or a medically qualified delegate) for review.
- The DMC will review the safety aspects of this study on a biannual basis.

- The CTU is responsible for the reporting of any unexpected serious transfusion related adverse cryoprecipitate reactions to the research ethics committee (REC), should any occur, and for preparing annual safety reports to the REC, on behalf of the Sponsor.

Statutory Reporting

Hospital staff remain responsible for reporting all transfusion related adverse events to SHOT/SABRE according to standard procedures, as required under the regulations of the EU Blood Directive.

SAE REPORTING

Within 24 hours of becoming aware of a reportable SAE, please scan and email to:
serious_adverse_events@nhsbt.nhs.uk

Quality Assurance and Control

Risk Assessment

A Risk assessment has been conducted which acknowledges the potential risks to the trial. This section provides an overview of the Quality Assurance (QA) and Quality Control (QC) measures that will be put in place to ensure the trial is performed and data generated and recorded in accordance with the principles of ICH GCP.

Central Monitoring at CTU

The CTU data managers will review all data received for errors and missing data points.

On-Site Monitoring

The frequency, type and intensity for routine monitoring and the requirements for “cause for concern” monitoring will be detailed in a separate monitoring plan.

Direct access to participant records

Participating investigators should agree to allow trial-related monitoring, including audits, ethics committee review and regulatory inspections by providing direct access to source data and documents as required. Participant consent must be obtained for this.

Confidentiality

Study data will be handled in accordance with the principles of General Data Protection Regulation (GDPR) and UK Data Protection Act 2018.

Auditing

In addition to potential GCP inspections or audits by the host R&D department, NHSBT CTU reserves the right to conduct site audits, either as part of its on-going audit programme, or in response to adverse observations during monitoring visits.

Statistical Considerations

Sample size

The CRYOSTAT-2 study is designed to detect an absolute mortality difference of 7% from a baseline mortality of 26%, i.e. a reduction to 19%. The baseline mortality chosen for CRYOSTAT-2 is based on several sources: the feasibility study CRYOSTAT-1 which reported a 28% mortality [26]; the national epidemiological study of trauma transfusion practice which reported a 39% mortality in patients receiving 10 or more units of RBC in 24 hours (classified as having 'massive haemorrhage') [14]; and the PROPPR study of bleeding trauma patients conducted at Level 1 trauma centres in North America [11] which had a baseline mortality of 26%.

CRYOSTAT-2 will evaluate a specific population of severely injured patients who will have a much higher background death rate than found overall in CRASH-2 [9]. The relative risk reduction for CRYOSTAT-2 should be considered alongside the findings in the CRASH-2 study which showed that TXA therapy improved mortality from bleeding, with an overall odds ratio of 0.71 (95%CI: 0.61 – 0.82). The potential observed mortality difference in CRYOSTAT-1 was 14%, and larger improvements were observed in cohort studies.

This study will use 90% power to detect a reduction in 28 day all-cause mortality of 7% using a 5% level of significance and a two tailed test. An initial blinded analysis after the first 300 participants have been recruited and followed-up to 28 days will allow us to reassess sample size requirements and recruitment rates, and if necessary modify the design of the study. A group sequential design has been used to allow for the Data Monitoring Committee reviewing the primary outcome for evidence of harm or benefit after 500 and 1000 participants have been followed-up for 28 days. Allowing for the interim analyses in this way, the required sample size to meet specified power requirements is 1530 participants in total. We initially increased this by 2.5% to allow for drop out, but drop out was higher than anticipated, so this was later increased to 4.4% leading to a total of 1600 participants.

Preliminary data from all 22 adult MTCs in UK show that MHPs are activated between 75-150 times every year at each site or approximately 1500 times per year nationally for trauma patients. Assuming a 25% recruitment rate, we would need to recruit 2 participants per month at each MTC to achieve a target of 380 participants per year in the UK (1142 participants in total over 3 years).

Target international recruitment is 140 participants per year (426 participants in total over 3 years) with accrual rates based on results from the recent PROPPR study [11] conducted at 12 centres in the USA and Canada.

Interim Monitoring and Analyses

An internal pilot phase will be completed 12 months from the date of the first recruited participant. We aim to open recruitment at 15 major trauma centres (MTCs) by month 6, and 22 MTCs by month 12. Recruitment will increase over the first 6 – 12 months whilst centres open, and we expect to randomise 93 participants by 6 months and 300 by 12 months. Our enrolment criteria for progression to the full trial will be i) stop if fewer than 200 participants are recruited at 12 months, ii) recruit additional centres if between 200-300 participants, iii) continue if at or above target (300 participants) at 12 months.

If the pilot determines the trial continues, an interim blinded analysis will be performed after 300 participants have been recruited and been followed up to Day 28. The primary purpose will be to confirm the sample size for the primary efficacy outcome of all-cause mortality. If the sample size is similar to, or less than, the sample size used to plan the trial, the trial will be continued until the required sample size of 1600 patients has been achieved. If the re-evaluated sample size is appreciably larger than 1600 in total (>5% larger), detailed consideration, involving the Trial Steering Group and the funding agencies will be given to whether it is clinically important, cost-effective and feasible to continue the study.

The Data Monitoring Committee (DMC) will monitor safety during the study and will inform the Trial Steering Committee (TSC) of any concerns regarding safety, futility or trial continuation. If the pilot and first interim analysis determine the trial continues, further interim analyses will be performed after 500 and 1000 patients have been recruited and followed-up for 28 days. At these points, O'Brien-Fleming stopping rules for harm or benefit will be used to guide the DMC review of the primary outcome data. The stopping rules will be used as a guideline, alongside the other safety data available to the DMC, and used as part of their overall assessment of the trial. They will have overall oversight and can recommend terminating the trial early for these or any other safety concerns.
Participant recruitment will be assessed each month throughout the trial with active measures taken at each centre to address any concerns over target enrolment rates.

Analysis Plan

The analyses will be described in detail in a full Statistical Analysis Plan. This section summarises the main issues.

Analysis of primary and secondary outcomes

At the first interim analysis, an updated estimate of the underlying mortality rate will be used to re-estimate the sample size [35]. This will be a blinded sample size re-evaluation using the overall event rate to estimate the variance of the primary outcome variable. At subsequent interim analyses, the standardised effect of the intervention on the primary outcome will be compared against O'Brien-Fleming stopping boundaries, preserving an overall significance level of 5% at the end of the trial.

All analyses will be performed on an intention to treat basis, and will include all randomised participants (including those randomised in error) on whom values of a response variable have been obtained. All analyses will be two-sided and the significance level will be 5%. The primary outcome, all-cause mortality at 28 days from arrival at hospital, will be determined as the proportion of participants in each treatment arm who have died within 28 days. The odds ratio for death within 28 days (with 95% confidence interval and p-value for the treatment arm term) will be presented, adjusted for centre using a random effect term, and this will be the primary analysis of the outcome. This will be supplemented by logistic regression analysis so that account can be taken of any factors (detailed in trial analysis plan) that may differ between the treatment arms. Mortality according to timing of cryoprecipitate administration will also be presented, using categories of ≤45 mins from arrival at hospital, 46 – 60 mins, 61 – 90 mins and over 90 mins. Mortality for those who did or not receive cryoprecipitate in the cryoprecipitate arm will also be presented.

As there is no placebo used in the study, per protocol analysis which excludes patients who do not receive trial treatment would differentially exclude those in the intervention arm. Per protocol analysis will therefore focus on the cohort of patients who could have

benefitted from the intervention and only exclude protocol deviations unrelated to the details of cryoprecipitate administration, randomisations in error, those who died within 90 minutes of admission and those who did not receive any blood products after arrival at hospital (an indication of those who had already stopped bleeding). Per protocol analysis will be presented for all mortality endpoints up to 28 days (6h, 24h and 28d), transfusion requirements, hospital stay and thrombotic events.

Multiple imputation based on full conditional specification will be used to impute values of potential risk adjustment factors. Particular attention will be given to the set of variables that will feature in the multiple imputation models. Primary and secondary outcome measures will not be imputed and these will be treated as missing data.

The methods used for the analysis of secondary outcomes in the form of proportions will be similar to that described for the primary outcome.

Survival times and rates will be estimated using the Kaplan-Meier method and compared using Cox proportional hazards regression. Transfusion requirements will be summarised as the median and interquartile range of the number of units administered from injury to 24 hours post-arrival at hospital. Hospital stay, critical care stay and ventilator days will be estimated using a competing risks analysis with discharge/extubation as the event and death as the competing risk.

The number of symptomatic thrombotic events up to day 28 will be presented overall and by treatment arm. In particular, the number of venous thromboembolisms (PE, DVT) and arterial thrombotic events (MI, stroke) will be calculated.

The primary outcome analysis will be repeated to assess the heterogeneity of treatment effects for the following subgroups:

a) UK participants vs non-UK participants
b) head AIS <4 vs ≥4
c) participant sex
d) participant age <70 vs ≥70 years
e) injury type blunt vs penetrating

The secondary outcome analysis of 6 and 24 hour mortality will also be repeated for subgroup analysis b) head AIS < 4 vs ≥4.

Health Economic Analyses

The health economic analysis will comprise comprehensive short-run and long-run analyses with full sensitivity analyses, plus a budget impact analysis and value of information analysis. A detailed analysis will be undertaken of the cost and cost-effectiveness of early cryoprecipitate plus standard of care versus the standard of care alone from an NHS and personal social services perspective. Within-trial analysis and long-run analysis will be undertaken, the former based on 28-day data in the trial (short-run analysis), the latter extrapolating beyond the end of the trial over the expected lifetime of the participant using pre-existing data (lifetime analysis).

In the short-run analysis we will focus on resource use and outcomes during the first 28 days only, and extrapolate beyond this period using modelling in the lifetime analysis. Our analysis will conform to accepted economic evaluation methods [36]. Costs in the short-run

analysis will take an NHS perspective. Those in the long-run will be based on the perspective of the NHS and personal social services (PSS). Costs will be presented in consistent prices, inflated where appropriate, and future costs and benefits beyond the first year will be discounted using recommended rates [36].

Analysis Population and Missing Data

Strategies to minimise the extent of missing data will include prompt review of data as it is received by data management and queries for missing or anomalous data. Data query resolution will be followed up by the data manager with assistance from the trial manager as appropriate.

In cases of discharge from hospital before day 28, data from the ONS will be used to determine the primary outcome wherever possible, otherwise those discharged from the major trauma centre will be inferred to be alive at 28 days and this inference tested in a sensitivity analysis. In the unlikely event that mortality data are still not available, or a patient is considered lost to follow up, the GP or participant will be contacted directly.

Where possible, missing outcome data will be inferred from other data available for a participant. Full details will be given in the Statistical Analysis Plan.

Ethical and Regulatory Issues

Compliance

This trial complies with the Declaration of Helsinki 2013. It will also be conducted in compliance with the approved protocol, the principles of Good Clinical Practice (GCP), the UK Data Protection Act and the National Health Service (NHS) Research Governance Framework for Health and Social Care (RGF).

Site Compliance

The site will comply with the above regulations and guidelines. An agreement will be in place between the site and NHSBT, setting out respective roles and responsibilities.

The site will inform the CTU as soon as they are aware of a possible serious breach of compliance, so the CTU can report the breach if necessary, within 7 days as per the UK regulatory requirements. For the purposes of this regulation, a serious breach is one that is likely to affect to a significant degree:

- The safety or physical or mental integrity of the subjects in the trial, or
- The scientific value of the trial.

Data Collection and retention

The Principal Investigator has overall responsibility for data collection at Sites on designated paper Case Report Forms. Participant data will be sent to NHSBT CTU for data entry onto the trial database, MACRO™, a commercially available FDA 21 CRF Part 11 compliant clinical trial database system produced by Elsevier. Following completion of analysis, the trial database will be archived in accordance with NHSBT's policies.

The sites must keep the signed Informed Consent forms, all trial documentation and source documents collected during the trial in a secure location (e.g. locked filing cabinets in a room with restricted access. All data must be accessible to the competent authorities, the Sponsor and NHSBT CTU with suitable notice for inspection. All trial documentation must be retained for at least 20 years after trial completion or termination. In addition, the Investigator must not discard or destroy any trial specific materials unless otherwise instructed by NHSBT.

Access to Data

Custody of the final data set will reside with the Chief Investigator and NHSBT CTU (for audit purposes). Access to the final data set for additional analyses will be permitted under the agreement of the Trial Steering Committee, according to the publication policy in section 16.

Ethical Conduct of the Study

Ethical Considerations

Before initiation of the trial at each clinical site, the protocol, all informed consent forms and any information to be provided to the prospective participant will be submitted to a Research Ethics Committee for ethical approval. Any subsequent amendments will be submitted to, and approved by, the same Research Ethics Committee.

Confidentiality

Trial data which is non identifiable will be collected at each site on the Case Report Form (CRF). Each participant will have a unique ID allocated to them which will be recorded on the CRF for reporting purposes. Only study sites and designated members of the research team authorised to do so, will have access to the identifiable information to maintain participant confidentiality. CRF data will be submitted to NHSBT CTU at pre-specified intervals and logged into the regulatory compliant, secure MACRO™ database. Only authorised personnel at NHSBT CTU will have password protected access to the study database.

Other approvals

The protocol will be submitted by those delegated to do so to the HRA for approval. A copy of the HRA approved Patient Information Sheet, Consultee Declaration Form, Patient Informed Consent Form and GP Information letter on local headed paper should be provided to the CTU before any participant is entered onto the study.

Indemnity

Indemnity for Centres

The sponsor will provide indemnity in accordance with the agreement with the trial centre. The investigator is required to have adequate current insurance to cover claims for negligence and/or malpractice. The sponsor will provide insurance cover for the clinical trial as required by national regulations.

Declaration of interests

None of the individuals named in this protocol have any competing interests to declare. The NHSBT CTU requires serving members of all Oversight Committees to sign a declaration of interests form on appointment and declare any competing interests which may develop during the conduct of the trial to be declared at the start of every meeting.

Oversight and Trial Committees

There are a number of committees involved with the oversight of the trial. These committees are detailed below.

Trial Management group (TMG)

A Trial Management Group (TMG) comprising the Chief Investigator, other lead investigators and members of the CTU. The TMG will be responsible for the day to day running and management of the trial. It will meet at least four times a year, more often during set up and close down phases of the trial. At least one face to face meeting will be held each year.

Trial Steering Committee

The Trial Steering Committee (TSC) has membership from the TMG and independent members, including the Chair. The role of the TSC is to provide overall supervision for the trial and provide advice through its' independent chair. The ultimate decision on continuation of the trial lies with the TSC.

Independent Data Monitoring Committee

The CTU has a core Independent Data Monitoring Committee (IDMC) for all of its trials, chaired by Professor Timothy Coats, University of Leicester. The group will act as IDMC to this study, provide advice to the Chair of the TSC and can recommend premature closure of the trial. For the purposes of this study, the core IDMC will be joined by an independent member who can provide expert disease specific advice.

Role of Study Sponsor

QMUL as Sponsor for the CRYOSTAT 2 trial is responsible for the initiation and management of the study, whereby activities are delegated to NHSBT CTU as appropriate.

Publication

Dissemination

The final study data set will be analysed and results published as soon as possible following completion of study follow up, final data checks and database lock. Individual Clinicians must not publish data concerning their participants that are directly relevant to questions posed by the trial until the Trial Management Group has published its report. The Trial Management Group will form the basis of the Writing Committee and will advise on the nature of publications

All outputs from the trial will be made publicly available via the CRYOSTAT-2 study website. Study findings will be presented to academic and non-academic groups. Our PPI group, PAIR, will play an important part in disseminating the study findings into the public domain. Dissemination to non-academic audiences including service users, commissioners, clinicians and service providers will be facilitated through the use of existing networks e.g. email lists, social media.

All research teams and PPI members involved in the study will be invited to a close out meeting to discuss the findings of CRYOSTAT-2. Surviving study participants will receive a trial completion newsletter summarising the main results of the trial. These networks will be utilised to drive traffic to a study website which will act as a repository of materials designed to increase the accessibility of research and to maximise impact. Main study findings will be published on the CRYOSTAT-2 study website as well as websites for the Centre for Trauma Sciences (C4TS), NHSBT and Bart's Charity with press releases available for newspapers and media websites.

Open access, peer reviewed academic outputs and research reports together with associated summaries and key findings will be produced for funders, policy makers and NHS audiences and held on the trial website. Data on longer term outcomes and health economic evaluation will be published after the 6 month follow up period has been completed. We will use email lists and Twitter to publicise and encourage active commentary on our outputs and to generate debate within the academic field. Other user friendly, innovative ways of packaging and disseminating findings will be investigated such as animations and video presentations.

Authorship and acknowledgements

Authorship for any publications arising from this study will follow the rules set out by the International Committee of Medical Journal Editors definitions of Authorship and Contributorship, http://www.icmje.org/ethical_1author.html

For the main report of this study submitted for publication, the members of the TSC and IDMC should be listed with their affiliations in the Acknowledgements/Appendix of the main publication and the support of the NHSBT CTU, and Funder acknowledged in all publications/presentations.

Approvals

Study results will be embargoed and not disseminated until authorised by the CI and TSC. Final manuscripts and presentations will be approved by the CI and TSC prior to publication. Similarly, any subsequent sub-study analysis will require authorisation by the

CI and TSC prior to publication. Sub-study manuscripts must not be published prior to the publication of the main study.

Identification

A trial identifier will be included on all presentations and publications. (ISRCTN14998314)

Protocol Amendments

Revision History:

Version	Author	Date	Reason for revision
2.0	Trial Management Group	03/07/2019	Clarification of consent processes for England and Wales. Clarification of continued follow up data in accordance with GDPR and CAG approval.
3.0	Trial Management Group	25/03/2021	Change in planned study duration. Addition of NI specific study processes. Addition of verbal and electronic consent of personal consultees and participants where obtaining a signed copy of the personal consultee declaration form or participant informed consent form would put staff and/or participants at risk of contracting COVID-19. Addition of the use of the PANDO Application for transfer of consultee declaration form and participant informed consent forms.
3.1	Trial Management Group	05/10/2021	Sample size changed to 1600; changes to the statistics section to reflect this.
4.0	Trial Management Group	15/02/2022	To reflect that Injury Severity Scores will be collected from TARN to ensure consistency with nationally reported scores. Additional data collection of baseline quality of life data from TARN where the research team have not been able to collect it in hospital.

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Appendices

Appendix A

Overview of consent procedure in England, Wales and Northern Ireland